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EARLY DEVELOPMENTAL STAGES OF THE HUMAN LUNG

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INTRODUCTION

The lung appears to be the last of the large organs of the human body about which a complete unquestioned embryological story has been built. In fact, the origin of the lung may be said to be as yet rather obscure.

In the latter part of the last century the theory was clearly expounded by Kölliker (1), Aeby (2) and His (3) that the entire lower respiratory passage (from larynx outward to and including the alveoli) arises as a diverticulum of the foregut.

This idea has led to much investigation in recent years and some doubt has been expressed as to its accuracy. From various observations a second theory has been developed which states that the lung may have a dual origin, such as has been shown to be the case in the kidney (Rose (4), Policard (5), Terni (6)). It has been postulated that the larynx, trachea, bronchi, bronchioles, and the part of the respiratory bronchioles lined with cuboidal epithelium arise from the foregut diverticulum while the remainder of the respiratory bronchioles, the alveolar ducts, alveolar sacs and alveoli arise from the mesenchyme into which the diverticulum branches. Assuming this theory to be true, the mode of union of these two embryonic components to form the completed tracheo-bronchial tree has never been demonstrated.

His (3), Narath (7), Merkel (8) and Blisnianskaja (9) carefully described the lungs in the human embryo but their accounts did not trace the development very far into the period of the foetus (third to ninth months inclusive). Thus there seems to be a need for more descriptions of developmental stages of the human lung. These studies are being made with

the idea that the nature of the tracheo-bronchial tree may be elucidated by tracing its development in a series of human embryos and foetuses. The lungs described in this paper complete the study to the 118 mm. C. R. stage. The first five specimens have been selected to form a well-spaced series as to crown-rump length. The original idea of continuing this rather close-spaced series was dropped because it appears that the description of lungs in the third month of prenatal development (foetuses from about 25 to about 75 mm. C. R. length) would only be a recitation of the continued growth of the epithelial anlage described in the first and second months of prenatal development. For a stage in the fourth month, a specimen was selected that shows excellent tissue fixation and that has a complete history. The menstrual age of this foetus was 109 days and the C. R. length is 118 mm.

In a recent paper the author (12) has rather fully described the human foetal lung at the 152 mm. stage (in the fifth month). The heart of this foetus beat for some minutes after delivery but there were no respiratory movements. The tracheo-bronchial tree at this stage has a continuous intact lining of epithelium and the maximum number of generations of tubules forming the tree is seventeen. The lining of the terminal tubules was a light-staining cuboidal epithelium, enclosing a small lumen.

The author is satisfied that a description of further stages in the gaps between 35 and 118 mm. C. R. length and between 118 and 152 mm. C. R. length would not add any essential facts to the story, and feels warranted in drawing the conclusion that the human tracheo-bronchial tree as found in the 152 mm. C. R. stage is entirely a product of the foregut entoderm. If there is a contribution from the mesenchyme to the human tracheo-bronchial tree it does not occur before the 152 mm. stage.

MATERIAL AND METHODS

The embryos that are described in this paper were selected from a large group on the basis of gross and microscopic appearance. The specimens were carefully measured in the crown-rump (C. R.) axis before sectioning. These measurements were:

Embryo I	11 mm.
Embryo II	15 mm.
Embryo III	19 mm.

Embryo IV..... 23 mm.
Embryo V..... 35 mm.
Embryo VI.....118 mm.

The specimens were fixed in formalin, imbedded, sectioned, mounted serially and stained routinely.

Wax reconstructions of the gross lung, of the complete tracheo-bronchial tree in Embryos II and IV, and of portions of the tree in the other specimens were prepared by projecting the sections on wax plates of the appropriate thickness. An Edinger projection apparatus was used.

A. MORPHOLOGY OF THE GROSS LUNG

LENGTH OF THE LUNGS: These measurements were taken either from the apex (superior pole) to the inferior pole as in Embryos I-IV, or from the apex to the posterior margin of the base as in Embryos V and VI.

	Right Lung	Left Lung
Embryo I.....	0.70 mm.	0.60 mm.
Embryo II.....	1.43	1.20
Embryo III.....	1.80	1.70
Embryo IV.....	2.08	1.80
Embryo V.....	5.08	5.24
Embryo VI.....	14.20	15.10

RIGHT LUNG (Plate I)

At the 11 mm. stage the right lung is an elongated loaf-shaped mass, flattened dorso-ventrad. At the 15 mm. stage the superior portion of this mass is the more bulky; the whole lung is the shape of an inverted pear. During the period from the 15 to the 35 mm. stages a sloping basal surface develops to replace the pointed inferior pole. As a result the shape of the right lung, while still piriform, is reversed, since the base of the pear is now downward. The sterno-costal surface of the right lung presents elevations at both the 11 and 15 mm. stages. During the 15 to 19 to 23 mm. intervals these elevations disappear over the superior and middle lobes, but traces of them are still present on the inferior lobe at the 35 mm. stage. By the time of the 118 mm. stage the right lung has the adult form, with entirely smooth surfaces.

LOBES AND FISSURES

1. *Superior Lobe.*—The anlage of the superior lobe at the 11 mm. stage is an ovoid lobule which faces dorsolaterad and which is incompletely separated from the anlage of the middle lobe. The groove partially separating these two lobes begins dorsad at the anlage of the oblique fissure and as the two lobes grow, extends ventrad. The superior lobe forms but little of the anterior border of the lung until the 19 mm. stage. From this latter stage to the 35 mm. stage, the superior lobe grows to a more anterior position. In effect, the superior lobe is rotated ventrad along the circumference of the inside of the thoracic wall during the 19–35 mm. interval, by the development of the inferior

lobe below and behind it. Meanwhile the superior lobe itself is growing and expanding laterad (Plate I). It appears that the superior lobe which arises from a more orally located portion of the right primary bronchus than do the middle and inferior lobes, is more mature than these latter lobes. The superior lobe at first grows dorso-laterad, then laterad and finally antero-laterad.

2. *Middle Lobe.*—The anlage of this lobe at 11 mm. is an incomplete lobule that faces directly laterad. By the time of the 15 mm. stage the lobule has grown ventrad to help form the anterior border of the lung. In the succeeding stages the middle lobe becomes relatively more inferior in position as the superior lobe develops above it, and more anterior in position as the inferior lobe develops below it. At the 35 mm. stage the superior lobe overhangs the middle lobe, but by the 118 mm. stage the middle lobe has become relatively larger in outline and more bulky, establishing the adult form. Thus it appears that the middle lobe grows at first directly laterad, then is carried downward by the growth of the superior lobe and rotated forward by the increasing mass of the inferior lobe. Finally, the middle lobe comes to lie in the angle between these two lobes. The adult position is inferior (in addition to anterior) because the superior lobe is more mature and bulky at each developmental stage than the middle lobe (Plate I).

3. *Inferior Lobe.*—At the 11 mm. stage the inferior portion of the loaf-shaped right lung represents the anlage of the inferior lobe. It is incompletely separated from and partly surrounds the middle lobe but is more completely marked off from the superior lobe. There are four elevations on the anlage of the inferior lobe, namely: one superior and dorsal, one superior and ventral, a third inferior and lateral and the fourth forming the inferior pole. At the 15 mm. stage the inferior lobe is more elongated and lies entirely inferior to the superior and middle lobes. The inferior pole has become more pointed. By the time of the 19 mm. stage the lower pole is being replaced by a surface. The posterior margin of this new surface is still sharply pointed. At the 23 mm. stage a sloping basal surface is present, and the lobe as a whole is pyramidal in shape with the apex at the superior end. The sterno-costal surface still presents elevations. These elevations are indistinct at the 35 mm. stage, and by the time of the 118 mm. stage the lobe with all surfaces smooth is a miniature of the adult inferior lobe.

4. *Oblique Fissure.*—At 11 mm. this fissure is represented by an incomplete and shallow groove. The anterior portion of this groove lies almost horizontal. By the 15 mm. stage this groove is much deeper, extends downward and forward, and makes a 30 degree angle with the horizontal. At the 15 and 19 mm. stages the oblique fissure is deepest at the point of junction with the transverse fissure. At the 23 mm. stage the oblique fissure makes a 45 degree angle with the horizontal due to the fact that the superior and middle lobes are farther developed than the inferior lobe at this stage. By the 35 mm. stage the oblique fissure is complete.

5. *Transverse Fissure.*—At 11 mm. the transverse fissure appears as a short groove extending from the anlage of the oblique fissure a

short distance ventrad and slightly upward. The fissure is complete at 15 mm. and at both this stage and at 19 mm. is deep in its posterior portion and shallow toward the front. By the time of the 23 mm. stage the *transverse* fissure is almost in that position, due to the rapidly increasing bulk of the superior lobe. This latter fact also accounts for the finding that the plane of the transverse fissure at the 35 mm. stage is directed upward as well as mesiad from the surface. In other words, the superior lobe overhangs the middle lobe. By the 118 mm. stage adult relationship has been developed.

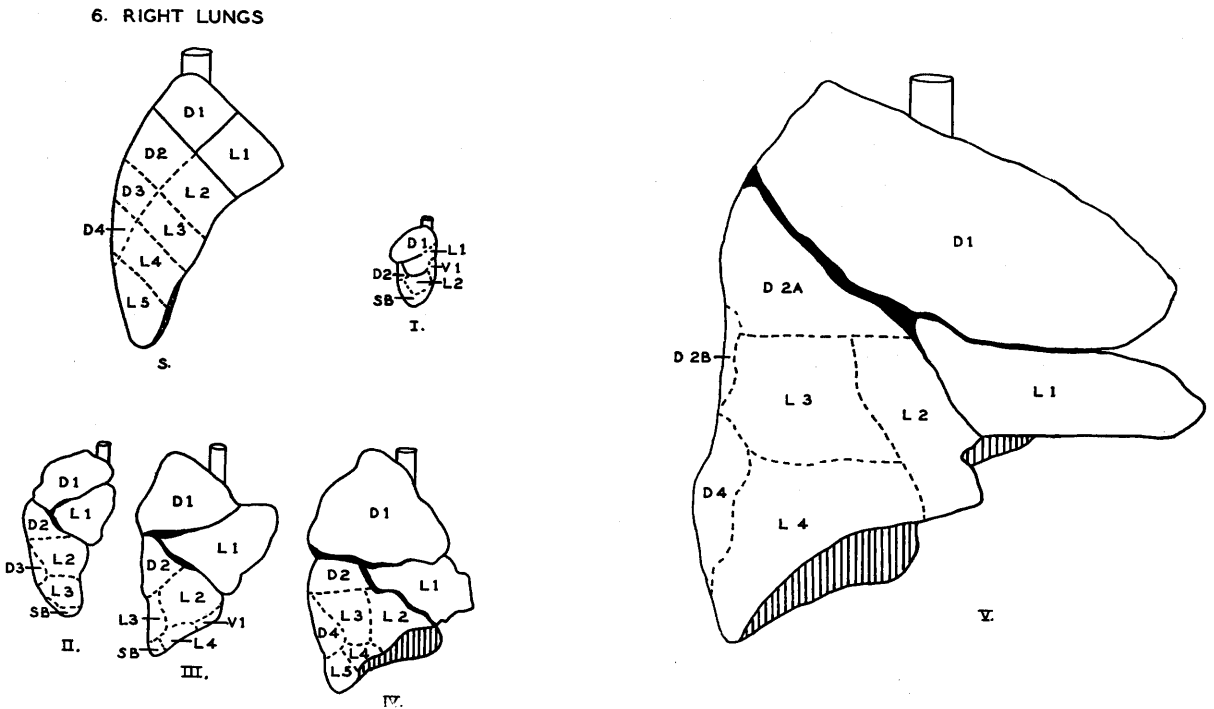
Left Lung (Plate II)

During the first two months of prenatal life the left lung is less elongated than the right, but early in the third month the situation is reversed, the left lung becoming and remaining the longer. In contrast to the six elevations on the right lung anlage at the 11 mm. stage, only five elevations are seen on the left lung. At each stage of the growth period under study, the superior lobe appears more mature than does the inferior lobe.

Lobes and Fissures

1. *Superior Lobe.*—The anlage of the superior lobe at the 11 mm. stage is an ovoid mass consisting of two conjoined lobules, a larger dorsal and a smaller ventral. These lobules are demarcated by a faint sulcus which is still present at the 19 mm. stage. At the latter stage the two lobules are of about equal size. At the 23 mm. stage the lobules are no longer distinct and the area corresponding to the ventral lobule is again smaller than the dorsal area. The groove between these two areas is very shallow at both the 23 and 35 mm. stages. At the latter stage a cardiac notch is present on the anterior border. At this stage this border and its notch lie directly lateral to the heart rather than anterior to it. At the 118 mm. stage the left superior lobe is a miniature of the adult specimen, with the exception of an incomplete fissure extending backward from the anterior border. This fissure begins just above the cardiac notch and extends backwards for 6 mm. but does not meet the oblique fissure. This additional fissure is to be regarded as an abnormality and not as a structure peculiar to the left superior lobe at the 118 mm. stage.

2. *Inferior Lobe.*—At the 11 mm. stage the anlage of the inferior lobe is an ovoid mass presenting three elevations, namely: a dorsal, a ventro-lateral and one formed by the lower pole. The depressions between these elevations are less distinct than those on the right inferior lobe at this stage. During the 11 to 19 mm. interval these elevations remain and enlarge, the entire inferior lobe becoming more bulky and less pointed at the inferior pole. At the 19 mm. stage there is only a slight indication of a basal surface. At 23 mm. an almost horizontal basal surface is developing. At 35 mm. the basal surface slopes farther downward in its posterior portion and the depressions and elevations on the sterno-costal surface are but faintly indicated. At 118 mm. the inferior lobe with all surfaces smooth has the adult form.

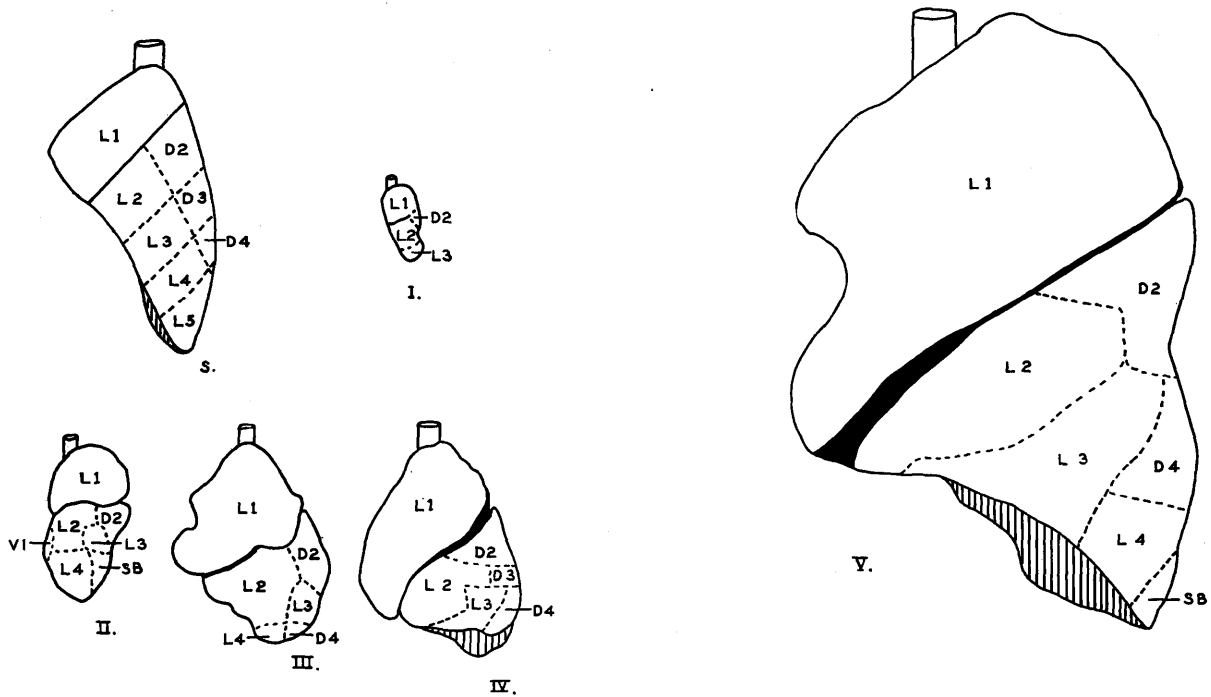


Schemata of the lateral aspects of reconstructions of the right lungs of Embryos I, II, III, IV and V, showing the areas supplied by the branch bronchi of the right stem bronchus. For comparison a schema (S) of the lobation of the lung, modified from Narath (7) is shown.

KEY: Margins and sulci—thin lines; fissures—heavy lines; plotted areas of branch bronchi distribution—dotted lines; diaphragmatic surfaces—parallel lines.

D1, D2, etc.—dorsal branch bronchi; L1, L2, etc.—lateral branch bronchi; V1—ventral branch bronchus; SB—stem bronchus.

7. LEFT LUNGS



Schemata of the lateral aspects of reconstructions of the left lungs of Embryos I, II, III, IV and V, showing the areas supplied by the branch bronchi of the left stem bronchus, compared with a schema (S) of the lobation of the lung modified from Narath (7).

KEY: Same as for Plate I.

3. *Oblique Fissure.*—At 11 mm. the anlage of the oblique fissure is almost horizontal. It is relatively deep except in its dorsal portion. At 15 mm. this fissure is complete. At 19 mm. its posterior portion is more obliquely placed. The oblique fissure is complete in respect to depth at 23 mm., and by the time of the 35 mm. stage has the adult relationships. (Plate II.)

B. TYPE AND DISTRIBUTION OF BRANCH BRONCHI

As the stem bronchi grow out into the mesenchyme and form the early lung anlagen, lateral buds known as branch bronchi arise from the walls of the stem bronchi. These buds may extend in any of the four principal directions, dorsal, lateral, ventral or medial. Those arising from the lateral aspect of the stem bronchus are the largest and most important group. These bronchi were termed "ventral" by Abey (2). They later extend more ventrad to supply the ventral portion of the lungs. However, His (3), Robinson (10) and Flint (11) term them "lateral or external" bronchi. The second most important group arise from the dorsal aspect of the stem bronchi. These are known as "dorsal" bronchi. Each dorsal bronchus (or group of dorsal bronchi in case more than one bronchus arises close together) usually arises orally to the corresponding "lateral" bronchus together with which it forms a "lung tier." The bronchi arising on the medial and ventral aspects of the stem bronchi are small and irregular. When present they are incorporated in the lung tier of that level. One exception to this statement is that one of the "ventral" bronchi found in the second "lung tier" is large. This has been called the infracardial bronchus. It usually becomes prominent in the right lung.

In the descriptions of these lungs the following nomenclature will be used: Dorsal bronchi (D1, D2, etc.); Lateral bronchi (L1, L2, etc.); Ventral bronchi (V1, V2, etc.); and Medial bronchi (M1, M2, etc.). In all cases a bronchus labelled (1) arises orad to a bronchus labelled (2) etc.

The patterns of the tracheo-bronchial trees are:

Branches of the right stem bronchus:

Embryo I—D1, L1, D2, V1, L2.
Embryo II—D1, L1, D2, L2, D3, L3.
Embryo III—D1, L1, D2, V1, L2, M1, L3, L4.
Embryo IV—D1, L1, D2, V1, L2, L3, D4, L4, L5.
Embryo V—D1, D2a, L1, D2b, V1, L2, L3, D4, L4.

Branches of the left stem bronchus:

Embryo I—L1, D2, L2, L3.
Embryo II—L1, D2, V1, L2, L3, L4.
Embryo III—L1, D2, L2, L3, M1, D4, L4.
Embryo IV—L1, D2, L2, D3, M1, D4.
Embryo V—L1, D2, L2, L3, D4, M1, L4.

No study was made of the tracheo-bronchial tree of Embryo VI.

A lateral view of the distribution of these branch bronchi is depicted in Plates I and II. It may be noted that the right stem bronchus of

Embryo II is the only stem bronchus that has a schematic distribution of branches; that is, it is the only stem bronchus from which the branches arise in an alterating pattern, first a dorsal branch bronchus, then a lateral branch bronchus. The other stem bronchi present a variety of patterns.

C. THE GENERATIONS OF BRONCHI

The determination of the exact number of generations of tubules present in the tracheo-bronchial tree, even in a very young embryo is a difficult problem. It is fairly well agreed that new tubules may arise by any one or by combinations of three methods, namely, lateral budding (monopodial), dichotomous branching and trichotomous branching. No definite regularity in the occurrence of these methods of tubule formation in the growing tree has been described. Furthermore, in examining an embryological specimen it should be remembered that the growth processes may have obscured the forms of earlier stages. A dichotomous branching may later appear to be a larger bronchus giving off a smaller side branch due to the more rapid growth of one of the pairs of bronchi previously formed by the dichotomous division.

In a previous paper (12) the author has described a method of estimating the number of generations present at any stage in the development of the tracheo-bronchial tree. This method requires the making of a wax reconstruction from serial sections of the lung.

In brief the method of enumeration is as follows: The primary bronchus is followed until its first branch is encountered. Then this branch bronchus is designated generation 2 and it is followed to the origin of its first branch. Now this branch is designated generation 3 and it is followed to the origin of its first branch. This is called generation 4 and the tracing is continued in this manner until the terminal blind-end tubule is reached.

Using this method the following determinations were made in the upper lobe of the right lung. The results were:

Embryo I—	11 mm.	3 generations
Embryo II—	15 mm.	5 generations
Embryo III—	19 mm.	6 generations
Embryo IV—	23 mm.	8 generations
Embryo V—	35 mm.	10 generations
Embryo VI—	118 mm.	14 generations

In all six of these tracheo-bronchial trees it is possible to trace the epithelium as a continuous intact layer from the lining of the trachea outward to the blind end of the terminal tubule that forms the last generation.

The epithelial lining of the tree in Embryos I, II, III, and IV is of a pseudo-stratified columnar type. The lining in the first eight generations of the tree in Embryo V is also of this type. The ninth and tenth generations of this latter tree is lined in most portions by a simple cuboidal epithelium; the remaining portions are like that of the first eight generations. In Embryo V we find the appearance of cartilage plates in the walls of the first three generations of bronchi. The first

eight generations of the tree in Embryo VI are lined by pseudo-stratified columnar epithelium, while the remaining generations (ninth through the fourteenth) are lined by a simple epithelium of a cuboidal type. Cartilage plates are found in the walls of the first six generations of tubules in Embryo VI.

Throughout the extent of the tree, in all of the specimens, the line of the basement membrane of the epithelial cells is distinct. The making of wax reconstructions showed that all of the cross-sections of tubules in an area were parts of the epithelial bronchial system springing from the trachea. The branching tubules in all of these lungs lie in the relatively avascular mesenchyme, which forms the major part of the lung in these stages. There was no formation anywhere in the mesenchyme that even faintly resembled a tubule developing from the mesenchymal tissue.

SUMMARY

1. The human tracheo-bronchial tree at the 118 mm. stage has a continuous intact lining of epithelium.

2. The tracheo-bronchial tree up to and including the 118 mm. stage appears to grow entirely as a branching of the original fore-gut diverticulum; the mesenchyme has no part in its formation during this developmental period.

3. According to a method of enumeration outlined, the number of generations in the tracheo-bronchial tree at the 11 mm. stage, three, increases to fourteen at the 118 mm. stage.

4. A lobe or a portion of a lobe that has its origin more orad on the primary bronchus is more mature at any period of development than a division that has its origin farther from the bifurcation of the trachea.

5. There is considerable variation in the pattern developed in the human tracheo-bronchial tree.

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